

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 9/14, 47/24</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/33817</b> <b>(43) International Publication Date:</b> 15 June 2000 (15.06.00)
<b>(21) International Application Number:</b> PCT/GB99/04070 <b>(22) International Filing Date:</b> 8 December 1999 (08.12.99)  <b>(30) Priority Data:</b> 9827006.9 8 December 1998 (08.12.98) GB 9925365.0 27 October 1999 (27.10.99) GB  <b>(71) Applicant (for all designated States except US):</b> PHARES PHARMACEUTICAL RESEARCH N.V. [NL/NL]; 14 John B Gorsiraweg, P.O. Box 3889, Curacao (AN).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> LEIGH, Steven [GB/GB]; Lucas & Co., 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB). LEIGH, Mathew, Louis, Steven [GB/GB]; Lucas & Co., 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB).  <b>(74) Agent:</b> COLE, Paul; Lucas & Co., 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHOSPHOLIPID COMPOSITIONS  <b>(57) Abstract</b>  The present invention relates to the preparation of powder or solid compositions comprising single and double chain amphiphilic lipids in association with polymers which harden them so that they can be comminuted into powder or granules. The compositions can act as carriers for biologically active compounds and can be administered to living organisms. Such a composition may comprise a biologically active compound and monoacyl and diacyl membrane lipid in association with a polymer, said composition being a solid that when stored in a glass container remains free flowing after 3 months at 40 °C and 75 % relative humidity. The lipids may be selected from those which have GRAS status e.g. enzyme modified lecithin, and the polymer may be selected from natural polysaccharide polymers, starches and their derivatives, cellulose and its derivatives and gelatines.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## PHOSPHOLIPID COMPOSITIONS

### Field of the invention

5

The present invention relates to the preparation of powder or solid compositions comprising single and double chain amphiphilic lipids generally. It particularly relates to lipid compositions comprising monoacyl and diacyl membrane lipid in association with polymers and biologically active compounds for administration to a living organism. Specifically, it describes the preparation of novel lipid polymer compositions that have improved physical characteristics and higher loading capacity for lipophilic and hydrophilic compounds. More specifically, it relates to stable membrane lipid compositions in particulate and in compact forms with superior bioavailability, suitable for oral and other applications.

15

### Background to the invention

#### Problem drugs

A major problem in delivering biologically active compounds to humans or animals concern poor absorption which may be due to:

20

(i) low solubility in aqueous media; and

(ii) poor membrane permeability.

These adversely affect bioavailability and reduce efficacy. The problem applies in particular to lipophilic compounds and presents a difficult challenge, particularly to the pharmaceutical industry from both technical and commercial perspectives. Commercially, the inability to improve bioavailability may be costly if the time to market approval is either delayed significantly or prevented. Indeed, numerous compounds that possess promising pharmacological activity are abandoned in the late stages of development because of poor and erratic bioavailability. In some

25

instances it may be possible to improve bioavailability by forming a derivative that is more hydrophilic without unacceptable changes in pharmacokinetics.

It is difficult to find a carrier system that improves the bioavailability of lipophilic compounds, which is efficient and non-toxic for oral administration and can be manufactured in conventional solid dosage forms. Ethanol and ethoxylated surfactants are widely employed in liquid compositions although there are serious limitations in their use. Another approach is to have the active material in a colloidal form or as a co-precipitate with the aim of improving dissolution characteristics. However, this may not completely solve the problem because the low membrane permeability may still defy efforts to improve bioavailability.

Problems of poor bioavailability are not limited to hydrophobic compounds. Some hydrophilic compounds with large molecular weights may give similar problems. Examples of hydrophilic compounds which are poorly absorbed include peptides e.g. insulin, peptidomimetic compounds, antibodies and genetic material e.g. oligosense nucleotides, etc. Poor bioavailability in these compounds may be due to degradation in the upper GI tract and low membrane permeability rather than low solubility.

Carrier systems are designed to improve delivery and maximise performance of active compounds. The system must be compatible with biological systems and able to deliver the active compound in a controlled manner. Above all, the components used must be non-toxic and conform to specifications that give reproducible performance. Although oral administration is the preferred route of medication, compounds are sometimes delivered via alternative routes e.g. inhalation, parenterally and transdermally. These routes can, however, create problems and are generally only considered when GI absorption is inadequate or cannot be controlled sufficiently. An efficient oral delivery system may provide the key to unlocking the clinical potential of problem compounds in drug discovery programmes. In this specification, delivery also includes absorption

across the buccal and other mucosa. By improving the bioavailability or controlling the release of potent drugs, toxicity may also be reduced because of the smaller doses that need to be given. For compounds that are expensive or available only in small quantities, it is an important consideration. The importance  
5 of delivery systems is widely recognised and the quest to improve and control bioavailability of problem drugs is one of the most active pursuits in pharmaceutical research.

#### Lipids as carriers for drugs

10

The benefits of using diacyl lipids, e.g. phospholipids as carriers for drugs and other biologically active materials are well known. Phospholipids are the major component of liposomes, microscopic vesicles for carrying biologically active compounds. The production of liposomes is discussed *inter alia* in EP-A-  
15 0158441.

More recently it has been proposed to use as carriers anhydrous systems based on monoacyl lipids or on mixtures of monoacyl and diacyl lipids. WO 98/58629 discloses a carrier system that comprises one or more monoacyl lipids or  
20 other related micelle-forming amphipaths, optionally in admixture with one or more bilayer forming diacyl lipids. The system is when prepared normally in the form of an anhydrous or near anhydrous solid, waxy solid or liquid and is contacted with aqueous fluid only in use or just prior to use. The effect of contact with aqueous fluid is that the carrier system is converted into drug-associated lipid  
25 particles that, depending on the ratios of diacyl and monoacyl lipids, may be in the form of liposomes, micelles or mixed micelles. At this stage, a lipophilic drug incorporated into the original carrier system may be present in a molecular form intercalated between the lipids making up the lipid aggregates (liposomes or mixed micelles) or may be held in the form of a totally micellar lipid-drug  
30 complex. The monoacyl components both promote solubilization of a biologically active compound in a mixture of monoacyl and diacyl lipids and aid dispersion

into small aggregates on contact with aqueous fluid. Where the carrier comprises a partially enzyme-digested diacyl lipid, bile salts and other emulsifiers are not required for release of the compound from the gastro-intestinal tract as the compound is largely in molecular dispersion in the partly digested lipid mixture.

5 However, as a bonus, dispersion into lipid aggregates may be further improved in the presence of emulsifiers such as bile salts particularly at 37°C.

A problem with which this invention is concerned is that lipids are generally not suitable for processing into solid forms under ambient conditions

10 except when used in small amounts. This is one reason that lipids, particularly phospholipids, are not used more widely as carriers in effective amounts.

#### Summary of the invention

15

An object of the present invention is to provide an improved carrier for hydrophilic and particularly for hydrophobic compounds that has pharmaceutical and industrial applications.

20

It is a further aim of the invention to provide a carrier composition that has superior bioavailability and is versatile, safe, efficient and cost effective to manufacture.

25

It is a further object of the invention to modify lipid components that are soft or waxy substances at ambient temperature, so that they can become hard (i.e. friable or crushable) and can be converted into free flowing powders that may be filled into hard gelatine capsules or the like, or may be compacted into solid forms e.g. tablets.

30

It is a further object of the invention to provide an extended range of lipid materials that may be converted into hard comminutable compositions.

The invention provides compositions in non-liquid form that are easy to prepare, and that may be solid compacts or may be particulate. Most preferably they are based on monoacyl and diacyl membrane lipids on their own or in admixture or a combination of membrane lipids with other single chain  
5 amphiphilic lipids. At least one solid hydrophilic substance, most preferably a polymer, is typically included in the composition.

At least one biologically active compound may be present in the lipid polymer associate. The active compound may be added to the solution or  
10 suspension of lipid and polymer before removal of solvent or it may be blended in with the lipid polymer associates after drying. In this case, the active compound may associate with the lipid polymer on hydration. Alternatively, the composition may be a mixture of e.g. two or more lipid polymer associates of different active compounds. Incompatible substances or compounds that work better when used in  
15 combination can be kept apart in separate lipid polymer associates. Separation of active compounds in this manner within the same dosage form would not be possible in aqueous solutions.

The lipid polymer associates have the potential to swell in water or other  
20 aqueous media to form viscous intermediate compositions, which may or may not be bilayered. Hydration may take place *in situ* e.g. from powders or granules inside a hard capsule or from a tablet in the GI tract and other mucosal surfaces. Depending on the proportions of monoacyl and diacyl lipid, polymer and other components present in the composition, the hydrated structure may further  
25 disperse in water and other aqueous media and reassemble into micelles, vesicles or mixtures of small lipid aggregates. Preference for the type(s) of small lipid aggregate formed depends on the properties of the biologically active compound and other requirements. Furthermore, release of a biologically active compound may take place from either the hydrated bulk structure or from the suspension of  
30 small lipid aggregates.

As far as the applicants are aware there has been no prior disclosure on phospholipids generally, particularly in the form of enzyme modified lecithin containing hydrolysed phospholipids with *GRAS* status to form solid lipid polymer associates and optionally with biologically active compounds, to improve oral  
5 bioavailability.

In this specification:

*lipid* refers to amphiphilic molecules based on, or containing, either one or  
10 two hydrocarbon chains and covers mixtures in addition to single compounds.

*Active Compounds* are *biologically* active substances that have a physiological or pharmacological effect in a living organism.

15 *Lipid associates* are complexed structures formed between the lipid and typically one or more hydrophilic polymers and optionally one or more active compounds. The active compound may be in molecular association or suspension in a lipid-polymer associate. Alternatively, it may simply be mixed with the lipid polymer associate. Lipid-polymer associates may be particulate with mean  
20 diameters typically between about 0.05mm to 5mm or they may be solid compacts.

*Small lipid aggregates* are polymolecular structures that may be formed when the lipid polymer associates come into contact with an appropriate aqueous  
25 medium. These structures may be vesicular, non-vesicular, micelles, reverse micelles, mixed micelles, or mixtures thereof.

#### Description of preferred embodiments

30 The present invention provides for compositions in compact and/or in particulate forms, comprising at least one micelle forming single chain amphipathic lipid and/or at least one bilayer forming double chain amphipathic



lipid and typically at least one polymeric material, optionally associated with an active compound.

### Particulate compositions

5

Particulate compositions according to the invention may take the form of particles or granules. Although particle size is not a limitation, the mean particle diameter of the solid lipid polymer associates is preferably between about 50  $\mu\text{m}$  to 5000  $\mu\text{m}$ .

10

Powder compositions may be obtained by milling or micronising using conventional equipment. Alternatively, the lipid polymer associates may be obtained as free flowing powders after spray drying and other suitable techniques to remove solvent. Powder compositions are suitable for filling into hard capsules or used as such. Fine free-flowing powders are towards the smaller end of the size range given above and typically have mean particle diameters between 50  $\mu\text{m}$  and 2000  $\mu\text{m}$ , preferably between 100  $\mu\text{m}$  and 1000  $\mu\text{m}$ , depending on the fill weight of the capsule.

20

Granular lipid polymer associates may be between 1mm to 5mm in diameter. The granules may be obtained by comminuting dried lipid polymer cake or by compacting powdered material into slugs and breaking them into granules. The granules may be used as such in various dosage forms or they may be further compressed into tablets.

25

### Tablets

30

Powders and granules may be compressed into tablets, lozenges, troches, buccal or mucosal tablets, pessaries, etc. Direct compression aids e.g. lactose, microcrystalline cellulose, dicalcium phosphate, etc. may be used if required. In other cases, small quantities of active compounds may be mixed directly with the lipid polymer associates for compression into tablets. By using appropriate

polymers and forming suitable associates, the invention enables waxy lipid materials to be compressed into tablets with good compression characteristics and properties e.g. uniformity of weight, hardness etc. The disintegration characteristics and dissolution profile depend largely on the type of lipid and polymer used to form the associates. Thus the tablets may either disintegrate rapidly or more preferably remain substantially intact in aqueous fluid, thereby allowing controlled delivery of active compounds in the gastro-intestinal tract and other sites. Lipid polymer tablets which have become hydrated e.g. by contact with saliva have good retention properties on mucosal surfaces and are particularly suited for mucosal e.g. sublingual and buccal delivery. They may be retained on mucosal surfaces for extended periods i.e. up to 12 hours or more depending on the type of lipid, polymer and lipid/polymer ratios. Other appropriate excipients that may be used are preservatives, flavourings, effervescent agents, glidants, lubricants, binding agents, disintegrating agents, flow aids, colorants, antioxidants, etc. The lipid polymer associates may be used e.g. in pharmaceutical, dietetic, food, toiletry, cosmetic, veterinary, aquaculture, horticulture and other industrial applications, or where there is need to improve the solubility of poorly water soluble compounds and/or enhance or control absorption of both water and oil soluble substances.

20

### **Lipid**

The lipids or other amphipathic materials that may be made hard by mixture with a polymer according to the invention may have a single hydrocarbon chain, may have two hydrocarbon chains or may, as is preferred, be a mixture of single-chain and two-chain materials. Preferred lipids are membrane diacyl lipids and their monoacyl derivatives but the definition also includes the mono- and di-esters and ethers of sugars and polyols, fatty acid esters and other fatty acid derivatives. These can hydrate and swell on contact with water to form lamellar or bilayered stacks. Generally, in excess water, above the critical micelle concentration (CMC) monoacyl lipids form micelles, whilst diacyl lipids above the phase transition temperature (T<sub>c</sub>) tend to arrange as bilayered vesicles or

30

reverse micelles. Preferred lipids are amphipathic membrane lipids e.g. phospholipids, glycolipids, ceramides, gangliosides and cerebroside.

Preferred compositions are compacts or powders comprising at least one  
5 monoacyl membrane lipid component. However, monoacyl and diacyl membrane lipids may also be used on their own. Most preferred compositions comprise mixtures of at least one monoacyl and at least one diacyl phospholipid. One or more charged monoacyl or diacyl lipids may be included to improve the association, hardness and hydration properties of the lipid-polymer associates. The  
10 compositions may comprise other single chain amphiphilic lipids in significant amounts in addition to phospholipids. Although it is preferred to have the active compound in molecular association with the lipid polymer, the active compound may also be in solid suspension. As a general rule, it is preferred to have lipophilic compounds in solid molecular solution, whereas hydrophilic compounds may be  
15 in suspension. Strongly hydrophobic compounds may require larger amounts of the single chain component or single chain component on its own for complete molecular solution.

Single chain materials preferably comprise a monoacyl derivative of a  
20 neutral or charged phospholipid, but it can also be a monoacyl derivative(s) of a glycolipid and sphingolipid. The lipids may be derived from natural plant, or animal or microbiological sources, synthesised or partially synthesised, including polyethyleneglycol (PEG) derived monoacyl phospholipids, e.g. pegalated monoacyl phosphatidyl ethanolamine. Examples of charged monoacyl  
25 phospholipids are the monoacyl derivatives of phosphatidic acid (PA), phosphatidyl inositol (PI), phosphatidylserine (PS) and phosphatidylglycerol (PG). Examples of neutral monoacyl phospholipids are the monoacyl derivatives of phosphatidylcholine (PC), phosphatidylethanolamine (PE) and sphingomyelin. Alternative amphiphilic single chain lipids e.g. fatty acid and alcohol, propylene  
30 glycol, glycerol, or sugar mono esters and their derivatives may also be used alone or preferably in combination. The hydrocarbon chain can either be unsaturated or saturated and can have between 10 to 24, preferably 14 to 18 carbon atoms.

The double chain lipid(s) is preferably a phospholipid but may also be mixtures with other amphiphilic diacyl lipids whose monoacyl derivatives have been mentioned above. Charged membrane lipids may also be used on their own or included in the mixture. The acyl chains can either be unsaturated or saturated  
5 and can have between 10 to 24, preferably 14 to 18 carbon atoms. Other membrane lipids, such as glycolipids, ceramides, gangliosides and cerebroside can be used in place of, or in partial replacement of phospholipids.

Although the lipid composition may comprise entirely of at least one or  
10 more single or double chain component on their own, preferably the weight ratio of single to double chain lipid in the mixture could be from 1:99 to 99:1, preferably between 1:25 and 25:1 and most preferably 1:10 and 10:1. It is also possible that lecithin containing high amounts of naturally occurring monoacyl lipid components within the aforementioned range may be used i.e. above about 3  
15 %w/w, preferably about 5 %w/w. Deoiled lecithin is an example of such a lipid blend. This may be obtained from either egg or soya bean. Mixtures of lecithin with fatty acid mono- and diesters and ethers of sugar, alcohol, polyglycerol and their derivatives may also be used.

20 In the case of phospholipids, instead of mixing pure fractions of the two lipids to obtain the target ratios, partially enzyme hydrolysed mixtures of lecithin that have the required proportions of the monoacyl to diacyl lipid components are particularly preferred. These phospholipid mixtures, which are known as enzyme modified lecithins are freely permitted in foods without restrictions and should  
25 thus present no problems for oral use. Wherever possible hydrolysed lecithin containing from 5 to 95 preferably 60 to 80 mole percent of monoacyl phospholipids obtained by enzyme hydrolysis with phospholipase A2 is preferred. The lecithin should be substantially pure and substantially free from non-polar lipids. Preferably the lecithin is GMO free or does not contain detectable levels of  
30 genetically modified components.

### Lipid:Active ratios

The quantity of lipid employed to form the associate depends on a number of considerations. These include the amount of active compound present and its physicochemical characteristics. The type and the charge of the lipid or lipid mixture are also factors to be considered. Where the invention is required to carry active compounds substantially in molecular association, higher amounts of lipid may be required to form the associates. Lipid: active compound ratios of 99:1 or even more may be employed in the case of extremely potent compounds or strongly hydrophobic problem drugs. In most cases, lipid: active ratios between 40:1 to 1:40 would be sufficient, depending on the type of lipid and the charge. Usually lipid: active ratios between 20:1 to 1:20 may be quite sufficient to (i) substantially solubilise lipophilic compounds or (ii) subsequently improve the bioavailability of both lipophilic and hydrophilic compounds.

15

Generally, less lipid is required to solubilise lipophilic compounds if higher proportions of monoacyl components are present, reducing the total amount of lipid in the composition. This is also the case where the active compound is hydrophilic and the lipid polymer composition is used mainly to control hydration and improve bioavailability at the site of absorption. Where the active compound is dispersed as discrete particles in the lipid polymer compositions, they should be less than 1µm, preferably below 250nm mean diameter.

### 25 Polymer

The compositions typically contain one or more polymer dispersible or soluble in hot water or an organic solvent. Water miscible polar solvents e.g. C2 - C6 alcohols, esters or ketones are preferred, although solvents that are non water miscible may also be used to disperse or dissolve the polymer. The amount of polymer employed may lie between 5%w/w to 90%w/w or more, preferably

10%w/w to 75%w/w depending on the required hardness and hydration characteristics of the lipid polymer associate.

The polymer may typically comprise less than 50% by weight of the composition. However, this is not a strict requirement. The polymer(s) is normally  
5 added as a solution in an organic solvent or hydrophilic medium and the solid lipid associate is formed after solvent removal. In cases where the polymer is water soluble, the solvent may be water. The definition of hydrophilic medium may also extend to sugars in some cases. Indeed, sugars can be regarded as a  
10 'solid' hydrophilic medium. This may be the reason why combinations of polymers and some sugars are particularly effective in hardening lipid. Mannitol, lactitol and xylitol and combinations thereof are suitable examples for use with polymers in the solid lipid compositions. Higher amounts of polymer produce compositions that are easier to turn into powders and granules and for subsequent  
15 compaction into tablets or the like. The compositions particularly in the form of a solid compact, also tend to take longer to hydrate and swell and are therefore more suitable for longer retention on mucosa e.g. buccal mucosa.

Water insoluble polymers may be dissolved or hydrated in an organic  
20 solvent e.g. ethanol, together with the lipid and the active compound to form a homogeneous solution or dispersion in the first instance. Where water-soluble polymers are used, they are dissolved/hydrated separately in water before adding to the organic lipid solution. Removal of the hydrophilic medium results in an anhydrous or nearly anhydrous solid lipid polymer association structure  
25 sufficiently hard to be micronised or turned into granules suitable for compaction, e.g. tablets. Alternatively, during removal of the hydrophilic medium, the composition may be spheronised or pelletised. Removal of the hydrophilic medium may be carried out by any suitable method, including vacuum drying, spray drying, lyophilisation or a combination of more than one method. Polymers  
30 allow lipids with a low melting point e.g. below about 30°C and natural unsaturated phospholipids with low phase transition temperatures that are

characteristically soft waxes at room temperature to be more easily handled for processing into solid and particulate forms. They also allow larger amounts of phospholipids to be used. Use of time dependent polymers with different swelling properties may modify hydration of the solid lipid associates in aqueous  
5 environment and offer a method to control and prolong the release of active compounds in the GI tract. Protection against hydrolysis and breakdown of the lipid and active compound in a low pH aqueous environment e.g. stomach, is possible if the polymer used is insoluble in acid medium. The lipid polymer associates may hydrate and swell when the pH is raised to release the active  
10 compound. In this way, drugs may be targeted to the lower regions of the GI tract.

Preferred polymers for hardening lipid are the natural gums and derivatives. They may also be synthetic polymers e.g. methacrylic polymers and copolymers, carboxy vinyl polymers and copolymers. Gelatine or partially  
15 hydrolysed gelatine may also be used. Most preferred polymers are the celluloses e.g. carboxy methyl cellulose, ethyl cellulose and combinations of cellulose with alginates or methacrylic polymers. Sodium alginate may also be employed on its own. Starches and modified starches e.g. maize starch, phosphated starch, pregelatinised starch, hydroxypropylated starch and starch sodium  
20 octenylsuccinate, etc, and those with a high amylose content are particularly suitable. Monoacyl phospholipids complex with amylose and form lipid associates that are harder and have good tolerability combined with good physical and chemical stability. They may be preferred for making lipid polymer associates to give improved bioavailability.

25

Charged polymers significantly increase lipid hardness. Some of the best lipid-hardening polymers have negatively charged carboxyl groups (such as sodium alginate and Eudragit L100 - methacrylic acid copolymer) or negatively charged sulphate ester groups (such as carrageenan). Charged molecules are  
30 generally more soluble in aqueous media, rather than organic solutions, and this is why there are more water-soluble polymers that can harden the lipid than ethanol-

soluble polymers. Generally, suitable lipid-hardening polymers that are ethanol-soluble are also soluble in aqueous media as well, at appropriate pH. Preferably, polymers should be dissolved or at least partially dispersed in a solvent before being dried with the lipid to increase hardness. Heat may be used.

5

Table 1 summarises the charge found on a number of common pharmaceutical polymers.

10 **Table 1.** Charge characteristics of a number of natural polysaccharide and synthetic polymers commonly used in the pharmaceutical industry.

Polymer	Charge	Ionic Group
Sodium carboxymethylcellulose (Carmellose sodium)	Acidic or anionic	Carboxyl
Alginic acid	Acidic or anionic	Carboxyl
Sodium alginate	Acidic or anionic	Carboxyl
Modified starches	Acidic or anionic	Carboxyl
Agar	Acidic or anionic	Sulphate Ester
Carrageenan	Acidic or anionic	Sulphate Ester
Gum arabic (Acacia)	Acidic or anionic	Carboxyl
Gum tragacanth	Acidic or anionic	Carboxyl
Gum xanthan	Acidic or anionic	Carboxyl
Pectin	Acidic or anionic	Carboxyl
Carboxypolymethylene (Carbomer)	Acidic or anionic	Carboxyl
Methyl Vinyl Ether / Maleic Acid Copolymer	Acidic or anionic	Carboxyl
Methacrylic Acid Copolymer	Acidic or anionic	Carboxyl
Ammonio Methacrylate Copolymer	Ionic Salt	Amino-chloride Salt
Basic Polymethacrylate	Basic or cationic	Amino
Chitosan	Basic or cationic	Amino
Starch	Neutral or nonionic	/
Hydroxyethylcellulose	Neutral or nonionic	/
Hydroxypropylcellulose	Neutral or nonionic	/
Hydroxypropylmethylcellulose (Hypromellose)	Neutral or nonionic	/
Gum guar	Neutral or nonionic	/
Carob bean Gum (Ceratonia)	Neutral or nonionic	/
Poly(vinyl alcohol)	Neutral or nonionic	/
Poly(vinylpyrrolidone) (Povidone)	Neutral or nonionic	/
Poly(oxyethylene glycols) (Macrogols)	Neutral or nonionic	/
Poly(oxypropylene) poly(oxyethylene) block copolymer (Poloxamer)	Neutral or nonionic	/

15        Polymers modify the physical characteristics of soft or waxy lipid substances. They also affect the formation of intermediate structures on hydration and conversion of these structures to small lipid aggregates in water or other aqueous medium. Biologically active compounds are found to have extremely high association in the anhydrous solid forms, the hydrated structures and where  
20        appropriate, the resultant aqueous dispersions of small lipid aggregates. Polymers further improve the association between the lipid and the active compound and



almost complete association between the lipid and the biologically active compound may be possible. They may improve chemical and physical stability and protect the lipid from oxidative and hydrolytic decomposition. Polymers provide solid lipid compositions that are tolerant to relatively large amounts of residual, adsorbed or deliberately added water without significant deterioration or changes in its physical properties such as flow properties, friability and softness. Powdered lipid polymer associates stored in glass containers remain free flowing after storage for 3 months at 40°C and 75%RH.

Most of the natural polysaccharide polymers, starches and their derivatives, cellulose polymers and gelatines are pharmaceutically acceptable for oral, mucosal, and topical administration. From their widespread use in food, they are not considered to represent a hazard to health. Table 2 summarises the physical characteristics and lipid hardening properties of some of the pharmaceutical polymers. It must be clearly understood that this is not an exhaustive list and other hydrophilic polymers not included in this list may also be suitable. Polymers may be used in combination and any suitable method of mixing and solvent removal can be employed to produce solid lipid polymer compositions on a commercial scale.

**Table 2 Examples of polymers that may be suitable for forming lipid polymer solids**  
**Characteristics of some pharmaceutical polymers, used in lipid polymer formulations.**

Polymer	Polymer Charge	Solvent Solubility	Lipid Hardening Properties	Reason For Lipid Hardening Properties
Sodium carboxymethylcellulose (Carmellose sodium)	Acidic or anionic	Dispersible in water Insoluble in ethanol	Very good, solid hard and dry	Carboxyl group on derivatised glucose monomers
Sodium alginate	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxyl group on guluronic acid and mannuronic acid monomers
Modified Starch	Acidic or anionic	Swellable in water	Very good, solid hard and dry	Carboxyl group
Agar	Acidic or anionic	Soluble in hot water Insoluble in ethanol	Very good, solid hard and dry	Sulphated agarose and agarpectin polymers with carboxyl groups on the glucuronic acid monomers of agarpectin
Carrageenan	Acidic or anionic	Soluble in hot water Insoluble in ethanol	Very good, solid hard and dry	Sulphated galactose and anhydrogalactose monomers
Gum arabic (Acacia)	Acidic or anionic	Soluble in water Insoluble in ethanol	Good, solid hard and dry	Carboxyl group on glucuronic acid monomers
Gum tragacanth	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxy group on galacturonic acid monomers
Gum xanthan	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxyl group on glucuronic acid monomers
Pectin	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxy group on galacturonic acid monomers
Carboxypolymethylene (Carbomer)	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxyl groups on synthetic polymer
Methyl Vinyl Ether / Maleic Acid Copolymer (Gantrez S)	Acidic or anionic	Soluble in water Soluble in ethanol	Very good, solid hard and dry	Carboxyl groups on synthetic polymer
Methacrylic Acid Copolymer (Eudragit L&S)	Acidic or anionic	Soluble in aqueous media > pH7 Soluble in ethanol	Excellent, solid hard, crispy and dry	Carboxyl groups on synthetic polymer
Ammonio Methacrylate Copolymer (Eudragit RL & RS)	Ionic Salt	Permeable in water Soluble in ethanol	Very good, solid hard and dry	Amino-chloride salt
Basic Polymethacrylate (Eudragit E)	Basic or cationic	Soluble in aqueous media < pH5 Soluble in ethanol	Very good, solid hard and dry	Amino groups on synthetic polymer
Chitosan	Basic or cationic	Soluble in aqueous media at very low pH Insoluble in ethanol	Very good, solid hard and dry	Amino group on derivatised glucose monomers
Starch	Neutral or nonionic	Swellable in hot water	Moderate	/
Hydroxyethylcellulose	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	/
Hydroxypropylcellulose	Neutral or nonionic	Soluble in water Soluble in ethanol	Moderate	/
Hydroxypropylmethylcellulose (Hypromellose)	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	/
Gum guar	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	/
Carob bean Gum (Ceratina)	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	/
Poly(vinyl alcohol)	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	/
Poly(vinylpyrrolidone) (Povidone)	Neutral or nonionic	Soluble in water Soluble in ethanol	Good,	Nitrogen atom of cyclic amide may form weak electrostatic interactions

5

It was found that the appearance of the composition was not significantly influenced by polymer concentration. Using the present processing and drying methods, a minimum amount of about 10% by weight of at least one polymer, based on the total weight of the solid composition, was required to substantially harden the soft lipid. High shear mixing, for example would allow the use of less water to give a homogeneous composition prior to water removal. Hot air or vacuum assisted drying methods are also efficient in reducing the processing time

and reducing residual water content to give stable and harder solid lipid compositions. However higher amounts of residual water up to about 30% w/w may be tolerated without adversely affecting hardness and other physical characteristics. Thus it may not be necessary to remove water entirely from the compositions. Any suitable method for drying and removal of solvent may be employed, including but not limited to e.g. fluidised bed drying, spray drying, freeze drying, supercritical fluid extraction, or a combination thereof.

#### Biologically active compound

The compositions may further comprise a biologically active compound which has lipophilic and/or hydrophilic properties. Preferably, it is in solution in the composition but it may also be in suspension.

Examples of biologically active lipophilic compounds include hydrophobic neutral cyclic peptides e.g. cyclosporin A. Taxol, tacrolimus or a macrolide e.g. a rapamycin, and derivatives thereof are also suitable examples. Examples of hydrophilic biologically active compounds include insulin, calcitonin and heparin. Another unrelated group of compounds which may be used with advantage are antioxidants, e.g. ubiquinone, tocopherols, carotenoids, and bioflavonoids. Other therapeutic classes of compound, may also be carried in the invention. The type and the concentration of active compound in the composition depend on the application and are not a limiting feature of the invention.

The invention will now described in the following examples, which illustrate *inter alia* the effect of varying the lipid and polymers on the formation and properties of the solid lipid associates, and the use of different lipid and polymers with and without biologically active compounds to obtain solid particulate lipid associates that may be used as such, as powders or granules, filled into hard capsules or the like, or compacted into e.g. tablets or the like. Furthermore, the lipid polymer associates have the potential to hydrate *in situ*, in

water or other hydrophilic media e.g. intestinal fluids, to form drug carrying small lipid aggregates with high entrapment and good bioavailability.

### Preparation of solid polymer lipid

5

#### Example 1

A solid associate containing cyA, phospholipid and a methacrylic acid copolymer was produced using a two-stage process. The first stage involved  
10 dissolving 5 parts of lipid, 1 part of drug and 2 parts of the polymer in a minimal quantity of ethanol. The lipid blend used in this formulation had a PC:MAPC weight ratio of approximately 33:66. The components were ultrasonicated at 50°C until an optically clear ethanolic solution was obtained. The second stage involved removing the ethanol by vacuum drying at 50°C for approximately 6 hours to  
15 produce a solid lipid polymer associate. The sample was weighed to a constant weight to ensure the complete removal of solvent from the associate. In this example the cyA was in complete molecular dispersion. The resulting associate was a friable light yellow solid, which could be comminuted into lipid/polymer granules about 1-2 mm in diameter. This powder was blended with 25% by weight  
20 of microcrystalline cellulose and the resultant composition was compressed into tablets that did not disintegrate in simulated gastric fluid.

#### Example 2

25 A solid associate containing cyclosporin, phospholipid and povidone was produced using the method described in Example 1. The required amounts of cyA (1 part by weight), lipid (5 parts by weight) and povidone (6 parts by weight) were weighed into a drying vessel. The PC:MAPC weight ratio of this lipid was approximately 33:66. The solid components were dissolved in a minimal amount

of ethanol by ultrasonication at 50°C. The optically clear yellow solution was vacuum dried to remove ethanol. The resultant associate was a firm glass-like solid that could be comminuted and that was suitable for filling into hard gelatine capsules. The cyA was in molecular solution in the lipid.

5

### Example 3

A nifedipine /phospholipid polymer associate was produced by dissolving 1 part by weight of nifedipine and 5 parts by weight of lipid (PC: MAPC weight ratio of 33:66) in a minimal amount of dichloromethane containing 2 parts by weight of a methacrylic copolymer (Eudragit L100) at room temperature. The resultant solution was subjected to vacuum drying until no dichloromethane could be detected. The resultant yellow solid associate was kept in the dark prior to hydrating in deionised water. A dispersion was produced by adding 0.2 g of the solid lipid complex to 10 ml of deionised water. The complex hydrated to form a viscous dispersion, where the nifedipine was substantially in solution and partially in suspension.

### Example 4

An associate containing griseofulvin, lipid (PC: MAPC weight ratio 33:66) and methacrylic acid copolymer was produced by suspending the griseofulvin in an ethanolic solution of polymer and lipid. The griseofulvin: lipid: polymer weight ratio was 10:5:2.5. The lipid: drug suspension was vacuum dried for 6 hours at 50°C to remove the ethanol. The resultant associate was an off-white flowable powder that may be compressed into tablets or filled into hard gelatine capsules.

### Example 5

A lipid associate containing lipid (PC: MAPC weight ratio 33:66): cyA : methacrylic acid copolymer at a ratio of 5:1:0.67 was prepared following the

30

method described in example 1. A hard, waxy solid was obtained that could be broken into granules. The powdered lipid associate remained in suspension in water below pH 6 and dissolved above pH 6. The cyA remained in molecular solution.

5

The methods used for forming the lipid associates described in examples 1 - 5 employ simple vacuum drying at elevated temperature, followed by a comminution process to break up the friable lipid complex into granules. Any appropriate method would be suitable for scale up. These include spray drying, lyophilisation, supercritical extraction and spray congealing.

10

#### Preparative method used in the following Examples

15

The solid lipid compositions prepared with active material and water-soluble polymers, were made using the following general method. Unless otherwise stated 5g of the dried lipid polymer composition was prepared in each case. Much larger amounts may be prepared by the use of appropriate equipment. The lipid and active (if present) were dissolved in ethanol. The polymer was hydrated in water which may be heated to about 50°C to obtain a viscous solution. The polymer solution was weighed into a glass jar and the lipid/ethanol/active dispersion was added. The mixture was stirred thoroughly until a homogenous gel formed. The gel was vacuum dried at 50°C/0.1mBar for ~24hours to remove all the ethanol and water.

20

25

#### Lipid type

#### Examples 6 - 7

30

Solid lipid polymer compositions shown below were prepared following the method described above using two different types of phospholipid which significantly differed in their phosphatidylcholine (PC) and monoacyl

phosphatidylcholine (MAPC) contents and sodium alginate. It was found that the appearance of the solids was influenced to some extent by the type of lipid used in the formulation. For example VP145 contains about 50% by weight of PC and 5% by weight MAPC, remainder glycolipid and other polar lipids, generally produced darker coloured and slightly firmer solids than equivalent formulations prepared with the lipid (VP 200) containing about 60% by weight MAPC and 40% PC. It is to be understood that in place of the VP145 and VP200 lipid used in the following examples, egg phospholipid containing 60% or more of PC may be used. Indeed 100% PC obtained either from egg, soya bean or other natural or synthetic sources may also be used on its own. The hardness of the resulting lipid polymer associates may be adjusted by varying the amount and type of polymer used accordingly.

Example No.	Sample	Dry Excipients	Appearance After Drying
6	VP145 lipid, sodium alginate polymer	VP145/Nystatin/ManugelLBB (50 : 2.5 : 47.5)	Golden brown crushable solid
7	VP200 lipid, sodium alginate polymer	VP200/Nystatin/ManugelLBB (50 : 2.5 : 47.5)	Yellow fine flowable powder

15

The powder in example 6 was ground in a mortar and pestle to produce a free flowing powder. 3g of the resultant powder were stored in 5ml glass vials at 40°C/75RH. After 6 months of accelerated storage, the powder remained free-flowing. In place of VP145 & VP200, egg phospholipid containing about 60% of PC may be used.

20

### Polymer type

25

### Examples 8 – 16

Several different polymers were used in examples 8-16 with VP145 lipid to establish the type of polymer that would be suitable for hardening the lipid. The solids were prepared using various concentrations of polymer, either in aqueous media, in ethanol or as a dry powder according to Example 6 and 7. The lipid was

30

dispersed in an equal amount of ethanol (w/w) before adding to the polymer. The experiments carried out are summarised in the following table.

Example	Sample	Dry Ratio	Appearance After Drying
8	No polymer	VP145	Golden wax
9	Gum Arabic	VP145/Acacia (70 : 30)	Golden slightly hard dry solid
10	Gum Xanthan	VP145/XanthanFN (70 : 30)	Light golden crispy hard solid
11	Carrageenan	VP145/GelcarinGP379N (70 : 30)	Light golden crispy hard solid
12	Methyl Vinyl Ether/Maleic Acid Copolymer	VP145/GantrezS-97BF (70 : 30)	Light golden crispy hard solid
13	Polyvinyl Alcohol	VP145/PVA (70 : 30)	Golden slightly waxy solid
14	Hydroxyethylcellulose	VP145/Natrosol250Gpharm (70 : 30)	Golden slightly waxy solid
15	Hydroxypropylcellulose	VP145/KlucelGFEP (70 : 30)	Golden slightly waxy solid
16	Sodium Carboxymethyl-cellulose	VP145/Blanose7LF (70 : 30)	Golden yellow hard solid flakes

5

The charge density on the polymer influenced the hardness of the lipid polymer associates. Gum arabic polymer, for example, consists of monomers of L-arabinose, D-galactose, L-rhamnose and D-glucuronic acid, in the approximate ratio of 3:3:1:1. Since only the glucuronic acid monomer is charged, the polymer has a low charge density and had only average lipid-hardening properties. Sodium alginate, on the other hand, consists of D-mannuronic acid and L-guluronic acid monomers, both of which are charged. This polymer has a high charge density and had very good lipid-hardening properties. Furthermore, the use of combinations of two or more polymers is not ruled out and may be preferred in some cases.

After drying at 50°C/0.1mBar the majority of the ethanol and/or water had been removed from the compositions to give a solid, crushable lipid polymer composition at room temperature. The solid composition of Example 16 was milled using a Culatti Mill with a 1 mm screen to produce a free flowing powder. The lipid polymer was compressed directly in a tablet machine to form compacts weighing approximately 400 mg. In a separate trial, the powdered lipid polymer composition was blended with three separate direct compression aids namely,



lactose, micro crystalline cellulose and calcium diphosphate and compressed into tablets. The ratio of lipid polymer associates to compression aid varied from 5% to 75% w/w. The tablets made were satisfactory.

- 5           The above examples are placebos to illustrate the invention and do not contain biologically active compounds. However, it is confidently predicted that both lipophilic and hydrophilic compounds may be used in the examples. Typically, lipophilic compounds would be dissolved or dispersed in the ethanolic lipid solution prior to combining it with the aqueous polymer solution.
- 10   Hydrophilic compounds may be in aqueous solution with the polymer. Lipid polymer associates with active compound in solid solution or dispersion are obtained on removal of the solvent.

#### Example 17

- 15           A lipid polymer associate composition comprising 20 parts of VP145 lipid and 15 parts of carboxymethyl cellulose and 5 parts of mannitol was prepared. The lipid was dispersed in a small amount of ethanol (w/w) before adding to the aqueous polymer and sugar solution. The slurry was dried under vacuum as in the
- 20   previous examples. A hard cake was obtained, which was milled in a Culatti mill using a 1mm screen. The powder collected was free flowing and mostly below 1mm average weight diameter. 1 part of Nystatin powder was uniformly blended with 49 parts of the powdered lipid polymer associate. The resulting composition may be used as such or it may be tabletted.

25

#### Polymer Grade

#### Examples 18-20

- 30           Solid lipid polymers were prepared with VP 145 lipid and Nystatin as the biologically active compound in a ratio by weight of 20:1. The lipid and active ingredient were dispersed in equal amounts of ethanol (w/w) and then added to an

aqueous solution of a polymer (Manugel LBB or Keltonel LVCR). In principle, there was no upper limit to how much water could be added to the lipid-nystatin-polymer compositions before drying, although large amounts of water required alternative processing methods e.g. spray drying. In practice, a minimum amount of water was necessary to produce a hydrated lipid polymer composition that was suitable for drying from slurry. The dried composition may be filled into hard gelatine capsules or the like or it may be tabletted.

Example	Sample	Dry Excipients	Appearance After Drying
18	No polymer	VP145/Nystatin (20 : 1)	Yellow waxy solid
19	47.5% Sodium Alginate	VP145/Nystatin/Manugel LBB (50 : 2.5 : 47.5)	Golden hard crushable solid
20	47.5% Sodium Alginate	VP145/Nystatin/Keltonel LVCR (50 : 2.5 : 47.5)	Golden hard flakes

### Hardness

#### Examples 21 - 24

The amount of polymer in the formulations below was varied to see how this affected the final hardness of the solid. The solids were prepared using a 4% or a 6% Keltone LVCR polymer solution and incorporated VP200 lipid and cyA as active ingredient in a ratio of 5:1. The lipid and active ingredient were dispersed in an equal amount of ethanol (w/w) before being added to the aqueous polymer solution. The solid compositions from Examples 23 and 24 were particularly suitable for powdering and filling into hard gelatine capsules. Each 500mg capsule contained 50mg of cyA. Alternatively the granules could be compressed into tablets.

Example	Sample	Excipients	Appearance After Drying
21	No polymer	VP200/CyA (83.33 : 16.67)	Yellow wax
22	10% Sodium Alginate	VP200/CyA/SodiumAlginate (75 : 15 : 10)	Yellow dry solid with a slight shine - can be broken up
23	20% Sodium Alginate	VP200/CyA/SodiumAlginate (66.67 : 13.33 : 20)	Yellow hard crispy solid - can be crushed
24	30% Sodium Alginate	VP200/CyA/SodiumAlginate (58.33 : 11.67 : 30)	Pale yellow hard crispy solid - can be crushed to flakes
25	30% Sodium Alginate 15% Xylitol	VP200/CyA/Na Alg/Xylitol (43.3 : 11.7 : 30.0 : 15 )	Extremely hard solid. Comminutable to fine powder.

5

### Flow Properties

#### Example 26

Components	Ratio w/w	Appearance after drying
VP200/NaCMC	50:50	Brittle yellow flakes

10            20 g of a lipid complex containing VP200 (50%) and NaCMC (50%) was produced in the usual manner. The dried lipid polymer associate was milled using a Culatti micro hammer mill through four screens with diameters of: 1 mm, 1.5 mm, 2mm and 4 mm. After milling all four powders uniformly filled into HGCs irrespective of the screen diameter. The resultant free flowing powders were sized

15            using Endecotts sieves. The particle size distribution of the four powders is provided in Figure 1. The powder milled through the 1.5 mm screen was filled into nine size 0 hard gelatin capsules using a Feton filler. The mass of powder inside the capsules was remarkably uniform. The mean capsule weight was 0.312g with a narrow standard deviation of 0.008 g.

20

### Stability of lipid

             Short-term stability studies were carried out to assay for degradation of the lipid both during manufacture and after storage of the lipid polymer solids. The

25            stability of the lecithin components PC and MAPC were followed by HPLC

analysis. During the manufacturing process the lipid was subjected to high temperature hydrolysing conditions for several hours which could easily have hydrolysed the PC initially to MAPC.I However, it was found that the lipid was stable both during manufacture and on storage of the lipid polymer solids.

5

#### **Association of active ingredient in solid lipid polymer compositions**

##### **Examples 27-30**

10       The examples below were prepared according to the method used in the previous examples. The association of the active material with the lipid was determined using analytical filtration. The assay for the active material was carried out by HPLC. The results indicate that near 100% association of the active material in the lipid polymer associates is possible even after up to 3 months  
15       storage at elevated temperature.

      A 40 g sample of the composition described in Example 27 was produced and ground in a mortar and pestle. Twenty 2g samples of this composition were stored in a 4ml glass vial. After 6 months storage the samples were physically and  
20       chemically stable. Under the conditions tested, after 6 months storage at 40°C/75%RH, the powder had a moisture content of about 15%w/w and still remained free flowing.

Example	Composition	Excipients	Association
27	Lipid/CyA/SodiumCMC	VP805/CyA/Blanose 7LF (50:10:40)	Initial --100% 1 month - 97.2% (4°C), 98.6% (25°C), 98.0% (40°C) 3 months - 98.8% (4°C), 98.5% (25°C), 98.8% (40°C) 6 months - 98.0% (4°C), 90.8% (25°C), 91.6% (40°C)
28	Lipid/CyA/Eudragit	VP805/CyA/Eudragit L100 (50:10:40)	Initial --100% 1 month - 97.9% (4°C), 97.2% (25°C), 98.1% (40°C) 3 months - 98.9% (4°C), 99.3% (25°C), 98.5% (40°C)
29	Lipid/CyA/Sodium Alginate	VP145/CyA/ManugelLBB (50:2.5:47.5)	Initial - 93.4% 1 month - 101.4% (40°C) 6 weeks - 102.0% (40°C)
30	Lipid/CyA/Sodium Alginate	VP805/CyA/ManugelLBB (50:2.5:47.5)	Initial - 96.2% 1 month - 100.0% (40°C) 6 weeks - 99.7% (40°C)

5

### Activity of lipid polymer solids

The activity of the drugs in the lipid polymer solids was assessed using a nystatin formulation. Nystatin was chosen because its activity could be assessed using simple *in vitro* microbiological assays. The antifungal properties of nystatin lipid solids were assessed using a cup-plate diffusion assay. The solids were diluted, in aqueous media to form lipid dispersions, which were compared to equal concentrations of a commercially available nystatin suspension, Nystan® (E. R. Squibb and Sons Ltd.). Tryptone-soya agar plates were used that had been inoculated with *Candida albicans* NCPF 3179 to a final concentration of 10<sup>6</sup> viable cells per ml. Solutions were incubated in 5.5 mm wells for 2 hours at room temperature, followed by 18 hours at 37°C. The zones of growth inhibition of the *Candida albicans* were measured and compared in Figure 2.

**Examples 31 – 33**

In Examples 31 to 33, three different starches were incorporated with VP200 lipid to illustrate the use of these polymers for hardening the lipid. The solids were prepared using various concentrations of polymer in aqueous media. In example 31, the lipid was dispersed in water without ethanol, before being added to the polymer. In examples 32 and 33, the polymers were dispersed in hot water prior to the addition of VP 200 dissolved in ethanol. Examples 31 to 33 are base compositions of solid lipid polymer. The biologically active compound may be added to the solution of lipid and polymer before drying or it may be blended into the dried lipid polymer powder to form a uniform mixture. The compositions may be powdered for filling into hard gelatine capsules or they may be formed into granules for tableting.

Example	Sample	Dried Ratio	Appearance After Drying
31	Starch sodium octenylsuccinate	VP200/ Starch sodium octenylsuccinate (1:1)	Pale yellow very crispy solid
32	*N-Lok™	VP200/ modified starch (1:2)	Pale yellow very crispy solid
33	*Crisp Film™	VP200/ high amylose modified starch (1:3)	Yellow crunchy solid

\*National Starch and Chemical Company

**Examples 34- 36**

Examples 34-36 illustrate the use of polymers generally for hardening a lipid widely used in food applications. Several different grades of gelatine were incorporated with de-oiled lecithin, which contains a mixture of neutral phospholipids, charged phospholipids and glycolipids. The solids were prepared using various concentrations of polymer in aqueous media. The lipid was dispersed in water without ethanol, before addition of the polymer to give a viscous dispersion. In all cases, removal of the water resulted in crispy compositions that could be further comminuted to give free-flowing powders or granules. The powdered lipid polymer compositions could be used in place of ordinary de-oiled lecithin in various applications, or they could be employed to

carry active compounds either in molecular association or dispersion with the liquid polymer.

Example	Sample	Dried Ratio Deoiled lecithin/Gelatin	Appearance After Drying
34	Alkali hydrolysed gelatine Bloom strength 200	1:1	Crispy film
35	Acid hydrolysed gelatine Bloom strength 150	1:1	Crisp film
36	Hydrolysed gelatine	1:1	Crisp, brittle film

5

### Examples 37 - 39

The following examples further illustrate the utility of the invention in rendering membrane lipids in combination with other polar lipids hard and comminutable to extend their use generally, particularly in oral dosage forms. In examples 37 - 39 the lipid was initially heated gently on a hot plate and the aqueous polymer solution was added and stirred to produce a homogeneous suspension. Removal of water from the slurry was carried out in a vacuum oven at 50°C until the weight of the composition remained constant. A hard, crushable solid polymer lipid composition was formed in each case. As in the previous examples, an active compound may be added to the slurry before removal of water or it may be blended into the solid polymer lipid powders after removal of water.

20

Example	Sample	Dried Ratio Lipid/polymer	Appearance After Drying
37	Phosphatidylcholine and saccharose monopalmitate	PC/saccharose monopalmitate/CMC (1:1:2)	Off white hard composition
38	VP200 and glyceryl monocaprylate	VP200 / glyceryl monocaprylate / maize starch (0.1:1:4)	Pale yellow friable solid
39	Egg phospholipid 60% PC and polyglyceryl monooleate	EPC/poly glyceryl monooleate/CMC (0.5:0.3:1.0)	Pale yellow crushable solid

## Examples 40 - 45

The following examples typically illustrate the utility of the invention in rendering various polar lipids and combinations thereof hard and comminutable to carry both lipophilic and hydrophilic compounds. Examples 40 - 41 are solid lipid polymer compositions comprising lipophilic compounds, that may be powdered and filled into hard gelatine capsules or with the aid of suitable excipients compressed into tablets. Examples 42- 43 are solid lipid polymer compositions comprising hydrophilic compounds. In example 40 the active, lipid and polymer were dissolved in dichloromethane to produce a clear yellow solution. The dichloromethane was removed from the solution under vacuum to produce a solid polymer composition containing flurbiprofen. In example 41 beclomethasone dipropionate was dissolved in an ethanolic solution of soya PC. The ethanolic solution was added to an aqueous dispersion of carboxy vinylpolymer and sodium carboxymethylcellulose. After drying, a crispy yellow solid composition of BDP was obtained. This composition could be further processed to produce a free flowing powder or granules. Examples 42- 44 were prepared by dispersing the active and lipid in an aqueous polymer solution. After drying, a hard, crushable solid polymer lipid composition was formed in each case. In example 44, acetic acid was added to the polymer solution to produce a solution of chitosan. In example 45, the cyA, EPC and methacrylic copolymer were dissolved in ethanol. A solid lipid polymer composition of cyA was obtained when the solvent was removed.

Example	Active compound	Lipid(s)	Polymer(s)	Dried Ratio Active/Lipid/polymer	Appearance After Drying
40	Flurbiprofen	VP 200	Eudragit E100	1:10:10	Slightly soft yellow solid
41	Beclomethasone dipropionate	Soya PC	Carboxy vinyl polymer/sodium carboxy methyl cellulose	1:20:2.5:20	Yellow crispy flakes
42	Chlorhexidine digluconate	Deoiled lecithin	Low molecular wt chitosan	1:5:10	Friable orange solid
43	Pancreatin	Deoiled lecithin	Carboxy methy cellulose	1:10:20	Off-white crispy solid
44	Heparin	VP145	Modified starch	0.1:1:2	Off-white friable solid
45	CyA	EPC (60%PC) polyglycerol monostearate	Methacrylic acid copolymer	0.1:0.5:0.2:0.2	Yellow crispy solid



The compositions in the examples may be filled into hard gelatine capsules or the like or alternatively, they may be compressed into tablets or the like.

### Presentation

5

The waxy nature of lipids has previously been a general obstacle to the use of effective amounts of lipid in solid dosage forms, which may be one of the reasons why more advantage has not been taken up to now of the capacity of lecithin to improve drug delivery. The use of polymers has now been shown to  
10 increase the hardness and modify the processing characteristics of lipid, which dramatically increases the potential use for such formulations. The present formulations can be incorporated into a number of delivery systems including solutions, suspensions, tablets, capsules, gels, suppositories and pessaries as well as a free powder or granules. The greater potential lies, perhaps, in compressing  
15 the powder into a tablet or filling it into a hard gelatine capsule for oral delivery.

20

## CLAIMS

1. A carrier composition for a biologically active compound comprising at  
5 least one single chain amphipathic lipid and/or at least one double chain  
amphipathic lipid and a polymeric material associated with and hardening said  
lipid or lipids.
2. The composition of claim 1, wherein at least the lipid components of said  
10 composition are materials which have GRAS (generally regarded as safe) status.
3. The composition of claim 1 or 2, comprising a monoacyl membrane lipid.
4. The composition of any preceding claim, comprising a diacyl membrane  
15 lipid.
5. The composition of claim 1 or 2, comprising an enzyme digested lecithin.
6. The composition of claim 5, comprising 60-80 mol % of monoacyl lipid.  
20
7. The composition of any preceding claim, wherein the polymer comprises a  
natural gum or a derivative thereof.
8. The composition of any preceding claim, wherein the polymer comprises a  
25 synthetic polymer.
9. The composition of any preceding claim, wherein the polymer has cationic  
or anionic groups.
- 30 10. The composition of claim 9, wherein the polymer has carboxyl or sulfate  
ester groups.

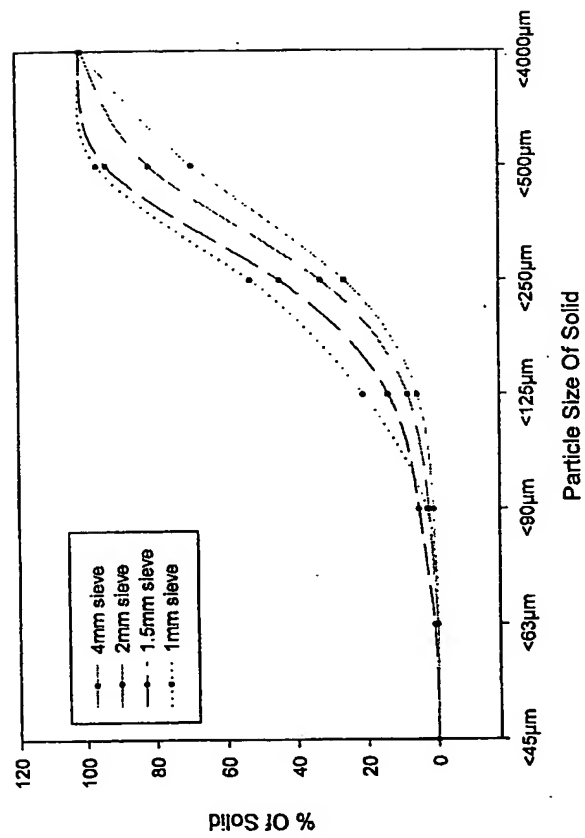
11. The composition of any preceding claim, wherein the polymer is selected from a salt of carboxymethylcellulose, alginic acid or a salt thereof, a starch modified with anionic groups, agar, carrageenan, gum arabic, gum tragacanth, gum xanthan, pectin, carboxypolymethylene, a methyl vinyl ether/maleic acid copolymer, an ammonio methacrylate copolymer, chitosan, a methacrylic acid copolymer, a hydrolysed gelatin.
12. The composition of any preceding claim, wherein there is present at least 10 wt % of the polymer based on the weight of said base composition.
13. The composition of any preceding claim, further comprising a sugar.
14. The composition of any preceding claim, further comprising a polyol, sucrose ester or polyglyceryl ester of a higher fatty acid or another polyol ester of a higher fatty acid.
15. The composition of any preceding claim, further comprising a biologically active compound.
16. The composition of claim 15, wherein the ratio by weight of the lipid to the active compound is from 40:1 to 1:40.
17. The composition of claim 15 or 16, wherein the active compound is present in molecular dispersion in the lipid.
18. The composition of claim 15 or 16, wherein the active compound is present as discrete particles in the composition.
19. The composition of claim 18, wherein the size of said particles is not more than 1  $\mu\text{m}$ .

20. The composition of any preceding claim, wherein the biologically active compound is cyclosporin A, Taxol, tacrolimus or a rampamycin.
21. The composition of any of claims 1-19, wherein the biologically active  
5 compound is insulin, calcitonin or heparin.
22. The composition of any preceding claim, wherein the biologically active compound is ubiquinone, a tocopherol, a carotenoid or a bioflavonoid.
- 10 23. The composition of any preceding claim, which is of powder of size 50-2000  $\mu\text{m}$ .
24. The composition of any preceding claim, which is of powder of size 50-1000  $\mu\text{m}$ .
- 15 25. The composition of any of claims 1-22, which is of granules of size 1-5 mm.
26. A method for making the composition of any preceding claim, which  
20 comprises dissolving or dispersing the ingredients in a solvent and removing said solvent.
27. The method of claim 26, wherein the lipid and biologically active compound (if present) are dissolved in ethanol, the polymer is dissolved in water,  
25 the aqueous and ethanolic solutions are mixed, and the mixture is dried.
28. The method of claim 26 or 27, comprising the further step of comminuting the composition after the solvent has been removed.
- 30 29. The method of claim 28, comprising the further step of forming said comminuted composition into a tablet.

30. The method of claim 28, comprising the further step of filling said comminuted composition into a capsule.
31. A lipid composition for administration to a living organism comprising a biologically active compound and monoacyl and diacyl membrane lipid in association with a polymer, said composition being a solid that when stored in a glass container remains free flowing after storage for 3 months at 40°C and 75% relative humidity.
32. The composition of claim 31, wherein the lipids are selected from those which have GRAS status, and wherein the polymer is selected from natural polysaccharide polymers, starches and their derivatives, cellulose and its derivatives and gelatines.
33. The composition of claim 1 or 31, wherein the lipid comprises natural lipid.
34. The composition of claim 1 or 31, wherein the lipid is an enzyme modified natural lipid.
35. The composition of claim 33 or 34, wherein the lipid is derived from egg or soya.
36. The composition of claim 1 or 31, wherein the lipid comprises partly synthetic lipid.
37. The composition of claim 1 or 31, wherein the lipid comprises synthetic lipid.
38. The composition of any of claims 33-37, wherein the polymer is selected from natural polysaccharide polymers, starches and their derivatives, cellulose and its derivatives and gelatin.

**Fig 1**

Size Distribution Of A Milled (Culatti Mill) Polymer Solid  
(VP805/SodiumCMC 50:50)





# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 99/04070

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K9/14 A61K47/24

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X, L	<p>WO 98 58629 A (PHARES PHARMACEUTICAL RESEARCH N.V.) 30 December 1998 (1998-12-30)</p> <p>page 16, line 9 -page 17, line 18 page 25 -page 27; examples 16-18 claims 17,18 document cited in the application the priority claim of the present application might not be justified</p> <p style="text-align: center;">--- -/--</p>	<p>1-6, 8, 12, 15, 17, 20-22, 26, 27, 31, 33-37</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

26 April 2000

Date of mailing of the international search report

09/05/2000

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Benz, K



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 99/04070

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 181 287 A (CIBA-GEIGY) 14 May 1986 (1986-05-14)</p> <p>page 2, line 5 -page 4, paragraph 2 page 7; example 2</p> <p style="text-align: center;">---</p>	<p>1,2,4,8, 15,18, 26,31, 33,35</p>
X	<p>EP 0 635 218 A (KAO CORPORATION ET AL.) 25 January 1995 (1995-01-25)</p> <p>page 5, line 39 -page 6, line 9 page 6, line 15 - line 19 page 9; example 1 page 14; example 12</p> <p style="text-align: center;">---</p>	<p>1-6, 14-16, 23,24, 26,28, 31,33-35</p>
X	<p>DE 195 31 277 A (BASF AG) 27 February 1997 (1997-02-27)</p> <p>the whole document</p> <p style="text-align: center;">---</p>	<p>1,2,4,8, 12, 14-17, 32,33, 35,38</p>
X	<p>DATABASE WPI Week 9440 Derwent Publications Ltd., London, GB; AN 1994-321236 XP002136412 &amp; JP 06 245719 A (NIPPON OILS &amp; FATS CO LTD), 6 September 1994 (1994-09-06) abstract</p> <p style="text-align: center;">---</p>	<p>1,2,4, 31-33, 35,38</p>
X	<p>DATABASE WPI Week 0296 Derwent Publications Ltd., London, GB; AN 1996-017127 XP002136413 &amp; JP 07 291854 A (TANABE SEIYAKU CO) abstract</p> <p style="text-align: center;">-----</p>	<p>1,2,7-9, 11,12, 15-17, 26,28, 30-33,38</p>

# INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No

PCT/GB 99/04070

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9858629	A	30-12-1998	GB 2326337 A AU 8118498 A	23-12-1998 04-01-1999
EP 181287	A	14-05-1986	AT 51152 T AT 84718 T AU 633844 B AU 4150489 A AU 586988 B AU 4934485 A CA 1249223 A CY 1677 A DD 244292 A DE 3587020 A DK 509485 A,B, EP 0346953 A ES 548492 D ES 8701491 A FI 854330 A,B, GR 852637 A HK 101192 A HK 192095 A HU 42936 A,B IE 63166 B IE 63156 B IL 76943 A JP 2037354 C JP 6048945 A JP 7068130 B JP 1844941 C JP 5058410 B JP 61204118 A KR 8900907 B MX 9203371 A NO 854403 A,B, NZ 214069 A NZ 229276 A PH 21673 A PT 81429 A,B SG 107192 G US 5002940 A ZA 8508481 A	15-04-1990 15-02-1993 11-02-1993 04-01-1990 03-08-1989 15-05-1986 24-01-1989 10-10-1993 01-04-1987 04-03-1993 07-05-1986 20-12-1989 01-12-1986 01-03-1987 07-05-1986 04-03-1986 24-12-1992 29-12-1995 28-09-1987 22-03-1995 22-03-1995 09-02-1990 28-03-1996 22-02-1994 26-07-1995 25-05-1994 26-08-1993 10-09-1986 13-04-1989 01-09-1992 07-05-1986 29-08-1989 29-08-1989 13-01-1988 01-12-1985 24-12-1992 26-03-1991 25-06-1986
EP 635218	A	25-01-1995	CN 1103234 A JP 6284866 A WO 9417675 A JP 7069932 A US 5785984 A JP 6316537 A	31-05-1995 11-10-1994 18-08-1994 14-03-1995 28-07-1998 15-11-1994
DE 19531277	A	27-02-1997	AU 6875396 A BR 9610234 A CA 2227272 A WO 9707786 A EP 0845982 A HR 960381 A	19-03-1997 29-06-1999 06-03-1997 06-03-1997 10-06-1998 28-02-1998
JP 6245719	A	06-09-1994	NONE	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/04070

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 07291854 A	07-11-1995	NONE	